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32 sub 91  
60. (Amended) The compound according to claim 59, wherein said polyethylene glycol has from about 2 to about 20 ethylene glycol subunits.

REMARKSStatus of the Claims

Claims 32-62 are pending in the present application and these claims are rejected under various sections of 35 U.S.C. Claims 50-62 are rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter not described in the specification in such a way as to reasonably convey to one of skill that the inventor had possession of the invention at the time the application was filed. Applicant responds to this rejection with traverse.

Claims 32-49 and 60 are rejected under 35 U.S.C. §112, second paragraph as being indefinite. The Examiner objects to Applicant's use of the term "structure" rather than "formula". Claims 32, 50 and 57 are amended to recited "[a] compound having the formula."

Claims 33, 34, 41, and 60 are rejected under 35 U.S.C. 112, second paragraph, for lack of antecedent basis. Applicant has amended claims 33, 41 and 60 such that they now include proper antecedent basis.

Claim 34 includes the recitation "said molecular energy acceptor" which is rejected as allegedly lacking antecedent basis. Proper basis for the phrase is found in claim 32 as filed at line 8.

Claims 32-62 are rejected as allegedly being obvious under 35 U.S.C. §103(a) over the combination of Meade et al. in view of Manoharan et al. and Gold et al.. Applicant responds with traverse.

Claims 32-61 are rejected over the combination of Nazarenko et al. in view of Templeton et al. Applicant responds with traverse.

Claim 32 is rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Nazarenko et al. A similar rejection over Meade et al. is also set forth.

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Applicant responds with amendment, replacing the word "structure" with "formula" and traverse.

### The Invention

Applicant has invented a nucleic acid probe having a molecular energy donor and molecular energy acceptor pair bound to the nucleic acid. The probe also includes a pair of stabilizing moieties that are attached to the nucleic acid probe. The stabilizing moieties function to bring the energy donor and the energy acceptor into operative proximity, thereby enabling transfer of energy from the donor to the acceptor.

When the nucleic acid sequence of the probe is not hybridized to a complementary nucleic acid strand, the probe emits minimal amounts of signal (e.g., fluorescence), because the energy donor is quenched by the energy acceptor of the unhybridized probe. The stabilizing moieties function to bring the energy donor and the energy acceptor into sufficient proximity that the quenching interaction can occur. When the nucleic acid portion of the probe is hybridized to a complementary nucleic acid strand, the interaction of the stabilizing moieties is disrupted, moving the energy donor and the energy acceptor to a distance away from each other that is sufficient to allow detection of signal emitted by the energy donor.

### The Rejections

#### Under 35 U.S.C. 112, first paragraph

Claims 50-62 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner alleges that a phrase from independent claim 50, "each CHOL interacts with the other CHOL to bring D and Q into operative proximity, thereby enabling transfer of energy from D to Q.", has no counterpart in the specification. Applicant respectfully traverses this rejection.

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The test for adequate written description for a later introduced claim element does not require the recitation of that element in *ipsis verbis*. The "claim limitation may be expressly, implicitly or inherently supported in the originally filed disclosure." MPEP §2163.05. The test is whether one of skill in the art would necessarily recognize that the Applicant had invented the claimed subject matter. *Heymes v. Takaya*, 6 USPQ2d 1448 (BPAI 1988), *aff'd* 10 USPQ2d 1473 (Fed. Cir. 1989). The initial burden of presenting by a preponderance of the evidence why a person of skill would not recognize in an Applicant's disclosure a description of the invention defined by the claims falls upon the Examiner. *In re Wertheim* 191 USPQ 90, 96 (CCPA 1976). Applicants respectfully submit that the burden has not been met for the following reasons.

At page 5, lines 19-20 of the specification as filed it is stated that,

"X and Y are the same or different  
and are non-nucleotide stabilizing  
moieties that interact to bring R  
and Q into operative proximity,  
thereby enabling transfer of  
energy from R to Q."

Thus, the specification includes a description of an interaction of two stabilizing moieties that brings the reporter (R) and quencher (Q) species into "operative proximity."

Moreover, the specification explicitly identifies cholesterol (CHOL) as a stabilizing moiety. For example, at page 6, line 15-16, there is found the statement:

...(D) is an exemplary stabilizing  
moiety (CHOL).

Furthermore, page 54, lines 8-9 includes the statement:

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[t]his CAP uses *two cholesterol stabilizing groups*, a fluorescein donor and a rhodamine acceptor.

Therefore, the specification explicitly identifies CHOL as a stabilizing moiety used in conjunction with a donor and an acceptor moiety, and provides an exemplary probe in which *two* cholesterol moieties are used as stabilizing groups to bring the reporter and the quencher into operative proximity.

In view of the evidence set forth above, Applicant has established the adequacy of written description sufficient to support claims 50-62. Therefore, Applicant requests the withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

**Under 35 U.S.C. 112, second paragraph**

Claims 32-34, 39, 41 and 60 are rejected under 35 U.S.C. §112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 32 is rejected under 35 U.S.C. §112, second paragraph, as being vague and indefinite. The Examiner states that it is unclear if the compound claimed reads on a formula as set forth in the claim or on a structure recited in one of these formulas. Applicant is unable to find any case law or rule of the Office that supports a rejection under 35 U.S.C. §112, second paragraph of a claim for including the term "structure" rather than the term "formula." To expedite prosecution, however, Applicant has amended claim 32 by replacing the term "structure" with "formula". Thus, Applicant requests withdrawal of the rejection.

Claim 39 is rejected under 35 U.S.C. 112, second paragraph, for not properly reciting a Markush group in Markush group format. Applicant has amended claim 39 to include the word "of", thus placing the claim in a proper Markush group format. Therefore, applicant requests withdrawal of the rejection.

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Claims 33, 34, 41, and 60 are rejected under 35 U.S.C. 112, second paragraph, for lack of antecedent basis. Applicant has amended claims 33, 41 and 60 such that they now include proper antecedent basis.

Claim 34 includes the recitation "said molecular energy acceptor" which is rejected as allegedly lacking antecedent basis. Proper basis for the phrase is found in claim 32 as filed at line 8.

**Under 35 U.S.C. 103(a)**

***Over Meade et al. in view of Manoharan et al. and Gold et al.***

The Examiner has maintained the rejection of claims 32-62 as being allegedly obvious under 35 U.S.C. §103(a) over the combination of Meade et al. in view of Manoharan et al. and Gold et al. that were advanced in the Office Action of May 30, 2001. The deficiencies of the combination of references were discussed at length in Applicant's previous response. Briefly, none of the references, either alone or in combination, disclose or suggest a nucleic acid that includes an energy acceptor (Q), an energy donor (R) and two stabilizing moieties that function together to bring the donor and acceptor into operative proximity. Without a disclosure or suggestion in the references of record of the claimed property, a proper *prima facie* case of obviousness cannot be set forth.

**A Prima Facie Case of Obviousness Cannot be Based Upon a Property That is Allegedly "Inherent" in a Combination of References**

The Examiner states that Applicant has not "clearly set forth sufficient argument as to why the modified compounds resultant from the combination of Meade et al. in view of Manoharan et al. and Gold et al. *would not possess the same properties as those compounds recited in the [of the] instant claims.*" The Examiner is, therefore, asserting that a compound that would result from the suggested combination of references would *inherently* possess the properties of Applicant's claimed compounds; namely, that

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the stabilizing moieties interact to bring R and Q into operative proximity, thereby enabling transfer of energy from R to Q.

A rejection for anticipation may rest upon a single reference that discloses all of the claimed elements of a compound or device, except for an element upon which novelty is premised, provided that the element is inherently present. Inherent anticipation requires that the missing element is "necessarily present," not merely probably or possibly present. *Trintec Industries, Inc. v. Top-USA Corp.*, 63 USPQ2d 1597 (Fed. Cir. 2002). The absence of an anticipation rejection of the pending claims, is an acknowledgment by the Office that the claimed structure did not exist prior to the Applicant's invention of it. Thus, the claimed structure and its properties are novel over the art of record.

In contrast to anticipation by inherency, the instant rejection presents a situation in which features of several references are isolated and combined. Applicant's claimed compounds, possessing the claimed property, are then alleged to be inherent in the combination.

It is well-established that a proper *prima facie* case of obviousness cannot rest upon inherency, because "inherency and obviousness are distinct concepts." *Kloster Speedsteel AB v. Crucible Inc.* 230 USPQ 81 (Fed. Cir. 1986). Moreover, "the inherency of an advantage and its obviousness are entirely different questions. That which is inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." *In re Sporman* 150 USPQ 449, 452 (CCPA 1966). See also, *W.L. Gore and Associates v. Garlock, Inc.* 220 USPQ 303, 314 (Fed. Cir. 1983). The art of record did not recognize that hydrophobic moieties conjugated to a nucleic acid alter the conformation of the nucleic acid, bringing acceptor and donor moieties attached to the nucleic acid within operative proximity. Thus, contrary to the mandate of the CCPA and the Federal Circuit, the present obviousness rejection is "predicated in what is unknown" and is, therefore, improper.

In another decision of the CCPA, *In re Wiseman*, 201 USPQ 658 (CCPA 1979) the rule is stated somewhat differently. In *Wiseman*, the Court held that an

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invention is obvious if it solves a problem and "the solution is obvious from the prior art which contains the same solution to a similar problem."

The art presently of record does not suggest that the configuration of a nucleic acid can be modified by conjugating hydrophobic moieties thereto. Moreover, at present, no art of record suggests that the conformation of a nucleic acid is, or can be altered by any species conjugated thereto, nor do any of the cited references suggest that groups attached to nucleic acid might be used to bring regions of the nucleic acid into proximity with each other. Furthermore, there is no art of record suggesting that the conformation of any species can be altered to bring energy acceptor and donor moieties into operative proximity by hydrophobic moieties attached to that species. Thus, it cannot fairly be said that the art suggests the "same solution to a similar problem."

The Examiner cites to two cases to support the obviousness rejection. The first of the cited case, *In re Best*, 195 USPQ 430, 433 (CCPA 1977) presents a situation distinguishable from that now at issue: in *Best* the claims were rejected as anticipated under 102(a) over a single reference that disclosed *all* the claimed elements with the exception of that element in which novelty was alleged to reside. A rejection under 35 U.S.C. §103 over the *anticipatory reference* was also advanced. The Courts have long "sanctioned the practice of nominally basing rejections on 103 when, in fact, the actual ground of rejection is that the claims are anticipated by the prior art." See, for example, *In re Pearson*, 181 USPQ 641 (CCPA 1974). Thus, the holding in *Best* is relevant only to those situations in which rejections under 102 and 103 are advanced simultaneously. As the present claims are rejected under 103 alone, and there is not anticipatory reference, the *Best* holding is inapplicable to the present situation.

The second decision relied upon is *Ex parte Obiaya*, 227 USPQ 58 (BPAI 1985), a decision of the Board of Patent Appeals and Interferences upholding a rejection under 35 U.S.C. §103 over a combination of references. The present rejection paraphrases the decision, "the fact that applicant has recognized another advantage which would flow from naturally from following the teaching of the prior art cannot be the basis for patentability when the differences would otherwise be obvious."

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In *Obiaya*, the applicant claimed a device that included a labyrinth heater. Labyrinth heaters were recognized in the art to maintain gaseous samples at a constant temperature. The applicant submitted evidence that the presence of the labyrinth heater resulted in a shorter response time for a detector downstream. The Board apparently concluded that one of skill would have recognized that a sample maintained at a constant temperature on its transit to a detector would reach the detector more rapidly than a sample that underwent fluctuations in temperature during the transit. Thus, the "advantage" recognized by the applicant flowed naturally from the teaching that labyrinth heaters maintain gaseous samples at a constant temperature.

For the decision in *Obiaya* to be applicable to the instant situation, there would have to be some recognition in the art that hydrophobic moieties could be used to bring together regions of a nucleic acid to which they were attached. In the absence of such a teaching, it cannot be said that Applicant's claimed property "flows naturally" from the prior art.

In contrast to Applicant's claimed invention, the art now of record teaches that cholesterol moieties on a nucleic acid probe *enhance the permeation* of the probes through cellular membranes, improving their intracellular delivery-not that the nucleic acid conformation is altered:

[i]t is an object of this invention to provide sequence-specific oligonucleotides having **improved transfer across cellular membranes**...In accordance with these and other objects, there are provided compounds that comprise a plurality of linked nucleosides wherein at least one of the nucleosides is functionalized...with...a **steroid** molecule, a reporter molecule...a non-aromatic lipophilic molecule... See, Manoharran et al., e.g., column 3, lines 15-35).



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The art of record is silent with regard to the ability of hydrophobic moieties *alter the conformation of the nucleic acid* to which they are attached such that an energy donor and acceptor are brought into operative proximity. Moreover, the art of record is silent concerning the general concept; no reference discloses that hydrophobic moieties *alter the conformation of a nucleic acid* to which they are attached. Therefore, the claimed "advantage" of Applicant's compounds cannot be fairly said to "flow naturally" from the teachings of the prior art as is required by the decision in *Obiaya*.

As the claimed property of Applicant's compounds was entirely unrecognized by the art, the present rejection must be based upon the conjecture that one skilled in the art would have known that hydrophobic stabilizing groups *necessarily* bring into proximity the regions of a nucleic acid to which they are attached, a conjecture unsupported by the record at present. None of the cited references support the conjecture. If the Examiner has taken judicial notice of this fact, the Applicant respectfully requests that the Examiner provide a reference indicating that the claimed property was notorious in the art. Alternatively, Applicant requests that the Examiner provide an affidavit supporting the alleged notoriety of the property.

As set forth above, the present obviousness rejection is improperly based on the principle of inherency. Therefore, Applicant respectfully requests the withdrawal of the rejection of claims 32-62 under 35 U.S.C. §103(a) Meade *et al.* in view of Manoharan *et al.* and Gold *et al.*

Claims 50-62 are Non-Obvious Over the Combination of  
References

As set forth above, the pending claims are non-obvious over the art of record and the combination set forth in the instant office action, because the rejection is improperly based upon the inherency of a property that is absent from the teachings of the art. In addition, claims 50-62 are further distinguished over the combination of references, as the art of record fails to suggest structures having the specific chemical formulae claimed by the Applicant. Moreover, the Office Action fails to provide explicit

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reasoning to support the rejection of claims 50-62. Of particular note is the absence of an argument based upon the specific structures that are explicitly set forth in independent claims 50 and 57.

In the previous Action, the Examiner stated that the Abstract of Manoharan et al. teaches that a substituent may be attached to "the internucleotide linkage linking the nucleoside to an adjacent nucleoside." Applicant does not disagree that the quoted statement is found in the Abstract of Manoharan et al. Although Manoharan et al. discuss methods for attaching substituents to the 2'-position, heterocyclic base, 5'-terminus, and 3'-terminus (*see*, columns 7-9), no method is provided for attaching a substituent to an internucleoside linkage.

Claims 50 and 57 set forth generic structures for the compounds of the invention in which the structures of the nucleic acid probes are explicitly set forth. Claims 50 and 57 set forth a species in which a stabilizing moiety and a donor or acceptor are attached to a common bi-antennary linker originating from a phosphodiester group. one antenna is attached to the stabilizing moiety; and the second antenna is attached to a second phosphodiester moiety. The second phosphodiester moiety is attached to a nucleic acid, which is attached to a second linker. The second linker is attached to either a donor or acceptor moiety.

As is surely appreciated by the Examiner, the genus of Manahoran et al. (substituents attached to "the internucleotide linkage linking the nucleoside to an adjacent nucleoside.") is of massive scope, potentially encompassing an infinite number of structures. For a reference to be utilized as the basis of an obvious rejection, it must suggest the compound claimed by the Applicant. "A disclosure of millions of compounds does not render obvious a claim to compounds." *See, In re Baird*, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). The Applicant asserts that, without the present specification to provide direction through the vast number of compounds suggested by Manoharan et al., one of skill would not be led to the claimed compounds. Moreover, Manoharan et al. does not disclose or suggest each of the elements of the claimed compounds of the present application. Thus, although Manahoran et al. may suggest a

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genus of nucleic acids in which a substituent is attached to an internucleoside bridge, the disclosure cannot fairly be said to suggest the specific structures set forth in claims 50-67.

Compounds of the claimed structure are not suggested by the cited art. Furthermore, the claimed compounds cannot be considered adjacent homologues of the compounds disclosed in the art. As the claimed compounds are neither disclosed nor suggested by the combination of cited references, a proper prima facie case of obviousness of claims 50-62 has not been set forth. Therefore, Applicant respectfully requests withdrawal of the rejection of claims 50-62 under 35 U.S.C. §103(a).

*Over Nazarenko et al. in view of Templeton et al.*

Claims 32-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nazarenko et al. in view of Templeton et al. Applicant respectfully traverses the rejection. In traversing the instant rejection, Applicant substantially reiterates the arguments made above: the claimed functional aspect of Applicant's compounds is neither suggested by the combination of the references, nor does it "flow naturally" from the teachings of the references. Moreover, regarding claims 50-62, the combination of the references fails to suggest the specific structures claimed by the Applicant. Therefore, Applicant respectfully requests the withdrawal of the present rejection.

The Office Action is Not in Compliance With 35 USC § 132

As discussed above, the combination of references fails to disclose several elements of Applicant's claims. Moreover, although the present Office Action states that claims 32-62 are rejected, *no specific grounds of rejection* are set forth for the dependent claims. For example, claims 41-42 set forth a composition of the invention including a hybridization enhancing moiety in addition to all of the other features recited in claim 32. No reference has been identified that suggests a compound of the invention that further includes the elements of claims 41-42 arranged as presently claimed. Moreover, claim 44 recites a composition of the invention attached to a solid surface-no reasoning has been advanced for the rejection of this claim. Regarding claim 51, no reference discloses or

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suggests the claimed linker moiety between the donor moiety (and acceptor moiety) and the nucleotide to which it is attached. Furthermore, as discussed above, no specific reasons are set forth for rejecting claims 50 and 57.

In view of the above shortcomings, the Office Action is not in compliance with 35 USC § 132, which requires that "[w]henever, on examination, any claim for a patent is rejected, . . . the Commissioner shall notify the applicant thereof, stating the reasons for such rejection . . . ." Similarly, 37 CFR § 1.104(a)(2) requires that "[t]he reasons for any adverse action or any objection or requirement will be stated and such information or references will be given." Therefore, should the Examiner maintain the present rejection of claims 50 and 57 and the dependent claims, the Applicant requests that the next Office Action be in compliance with 37 CFR § 1.104(a)(2) and that the record be explicitly clarified regarding the reasons underlying the finding of obviousness for each of the rejected claims. Moreover, Applicant requests that the elements of the each of the claims be located in the art or that reason be provided for why it is not necessary to locate each of the elements in the art.

**Under 35 U.S.C. 102(b)**

Claim 32 is rejected under 35 U.S.C. 102 (b) as being anticipated by Nazarenko et al. This rejection was based upon the use of the word "structure" in claim 32. Applicant has amended claim 32 to replace the word "structure" with the word "formula". Thus, applicant requests withdrawal of the rejection.

**Under 35 U.S.C. 102(e)**

Claim 32 is rejected under 35 U.S.C. 102 (e) as being anticipated by Meade et al. This rejection was based upon the use of the word "structure" in claim 32. Applicant has amended claim 32 to replace the word "structure" with the word "formula". Thus, applicant requests withdrawal of the rejection.

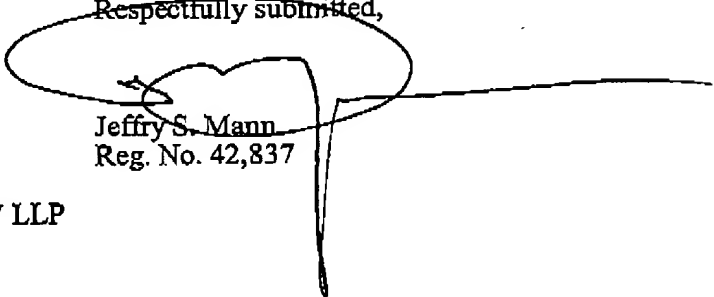
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CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 415-576-0200.

Respectfully submitted,

  
Jeffrey S. Mann  
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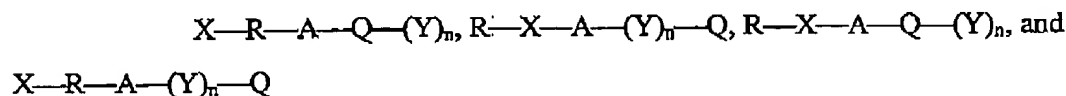
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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

32. (Amended) A compound having a [structure] formula which is a member selected from the group:



wherein,

A is a nucleic acid chain comprising nucleic acid monomers selected from the group consisting of natural nucleic acids, modified nucleic acids and combinations thereof;

R is a molecular energy transfer donor;

Q is a molecular energy acceptor; and

X and Y are the same or different and are non-nucleic acid stabilizing moieties that interact to bring R and Q into operative proximity, thereby enabling transfer of energy from R to Q; and

n is 0 or 1.

33. (Amended) The compound according to claim 32, wherein said molecular energy transfer donor is a fluorophore.

39. (Amended) The compound according to claim 32, wherein said nucleic acid monomers are joined by linkages that are members independently selected from the group consisting of phosphodiesters and modified phosphodiester.s.

41. (Amended) The compound according to claim 32, wherein said nucleic acid [sequence] chain further comprises a hybridization enhancing moiety.

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$$\text{D-R}^5\text{HN}-\text{Nu}^1-\text{O}-\text{P}(=\text{O})(\text{O}^-)-\text{O}-\text{CH}_2-\text{CH}(\text{CHOL}-\text{Y}^1)-\text{O}-\text{P}(=\text{O})(\text{O}^-)-\text{O}-\text{CH}_2-\text{CH}(\text{Y}^2-\text{CHOL})-\text{O}-\text{P}(=\text{O})(\text{O}^-)-\text{O}-\text{Nu}^2-\text{NH-R}^6-\text{Q}$$

60. The compound according to claim 59, wherein said [PEG] polyethylene glycol has from about 2 to about 20 ethylene glycol subunits.